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1998wo-us14552.ap.	1

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<u>L3</u>	1998wo-us14552.ap.	1	<u>L3</u>
<u>L2</u>	1998wo-us12456.ap.	1	<u>L2</u>
<u>L1</u>	1998wo-us12456.ap,prai.	80	<u>L1</u>

END OF SEARCH HISTORY

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/00, C07K 14/705, 16/28, 19/00, A61K 38/00, A01K 67/027	A1	(11) International Publication Number: WO 99/10484 (43) International Publication Date: 4 March 1999 (04.03.99)
(21) International Application Number: PCT/US98/14552 (22) International Filing Date: 14 July 1998 (14.07.98) (30) Priority Data: 08/918,874 26 August 1997 (26.08.97) US (71) Applicant: GENENTECH, INC. [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US). (72) Inventors: ASHKENAZI, Avi, J.; 1452 Terrytown Street, San Mateo, CA 94401 (US). GURNEY, Austin; 1 Debbie Lane, Belmont, CA 94002 (US). (74) Agents: MARSCHANG, Diane, L. et al.; Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080-4990 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: RTD RECEPTOR (57) Abstract Novel polypeptides, designated RTD, which are capable of binding Apo-2 ligand are provided. RTD are receptors for the tumor necrosis factor (TNF), belonging to the family of trail - receptors. They are inhibitors of APO2L- induced apoptosis. They act as decoy receptors, lacking an intracellular signalling death domain. Compositions including RTD chimeras, nucleic acid encoding RTD, and antibodies to RTD are also provided.		

apoptosis. Similar results were obtained with HeLa cells (data not shown). These results suggest that RTD does not signal cell death and demonstrate that RTD can inhibit Apo-2 ligand function when it is expressed at high levels.

EXAMPLE 5

Northern Blot Analysis

Expression of RTD mRNA in human tissues was examined by Northern blot analysis. Human RNA blots were hybridized to a 200 bp ³²P-labelled DNA probe based on the 3' untranslated region of the RTD. The probe was generated by PCR with the following oligonucleotide primers: CTTTCAGGAAACCAGAGCTTCCCTC (SEQ ID NO:4); TTCTCCCGTTTGCTTATCACACGC (SEQ ID NO:5). Probes specific for beta-actin were used as controls. Human fetal RNA blot MTN (Clontech) and human adult RNA blot MTN-II (Clontech) were incubated with the DNA probes. Blots were incubated with the probes in hybridization buffer (5X SSPE; 2X Denhardt's solution; 100 mg/mL denatured sheared salmon sperm DNA; 50% formamide; 2% SDS) for 60 hours at 42°C. The blots were washed several times in 2X SSC; 0.05% SDS for 1 hour at room temperature, followed by a 30 minute wash in 0.1X SSC; 0.1% SDS at 50°C. The blots were developed after overnight exposure by phosphorimager analysis (Fuji).

As shown in Fig. 4, a single RTD mRNA transcript of about 4 kb was detected. This transcript was expressed in fetal kidney, liver and lung, and in multiple adult tissues, particularly in testis and kidney. This mRNA expression pattern differs from that of DR4, DR5 and DcR1. DR4 and DcR1 are particularly abundant in peripheral blood leukocytes and spleen, and DR5 is most abundant in ovary, liver and lung.

EXAMPLE 6

Chromosomal Localization of the RTD, DR5, DR4 and DcR1 genes

Chromosomal localization of these human genes was examined by radiation hybrid (RH) panel analysis. RH mapping was performed by PCR using a human-mouse cell radiation hybrid panel (Research Genetics) and primers based on the coding region of the DR5 cDNA [Gelb et al., *Hum. Genet.*, 98:141 (1996)]. Analysis of the PCR data using the Stanford Human Genome Center Database and the Whitehead Institute for Biomedical Research/MIT Center for Genome Research indicates that DR5 is linked to the marker D8S481, with an LOD of 11.05; D8S481 is linked in turn to D8S2055, which maps to human chromosome 8p21. A similar analysis of DR4 showed that DR4 is linked to the marker D8S2127 (with an LOD of 13.00), which maps also to human chromosome 8p21. Analysis of DcR1 using radiation hybrid panel examination showed that the DcR1 gene is linked to the marker WI-6536, which in turn is linked to D8S298, which maps also to human chromosome 8p21 and is nested between D8S2005 and D8S2127.

Using a primer based on the 3' untranslated region of the RTD cDNA, an analysis revealed that RTD was linked to marker SHGC-33989 (LOD of 7.2). Marker SHGC-33989 is linked to D8S2055, which maps to human chromosome 8p21. Thus, the human genes for RTD, DR5, DcR1 and DR4, all map to chromosome 8p21.

Deposit of Material

The following materials have been deposited with the American Type Culture Collection, 10801 University Blvd., Manassas, Virginia, USA (ATCC):

<u>Material</u>	<u>ATCC Dep. No.</u>	<u>Deposit Date</u>
pRK5-35663	209201	Aug. 18, 1997
pRK5-35664	209202	Aug. 18, 1997

5 This deposit was made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposit will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying
10 open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC §122 and the Commissioner's rules pursuant thereto (including 37 CFR §1.14 with particular reference to 886 OG 638).

15 The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

20 The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting
25 the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANT: Genentech, Inc.
- (ii) TITLE OF INVENTION: RTD Receptor
- 5 (iii) NUMBER OF SEQUENCES: 5
- (iv) CORRESPONDENCE ADDRESS:
- (A) ADDRESSEE: Genentech, Inc.
- (B) STREET: 1 DNA Way
- (C) CITY: South San Francisco
- 10 (D) STATE: California
- (E) COUNTRY: USA
- (F) ZIP: 94080
- (v) COMPUTER READABLE FORM:
- (A) MEDIUM TYPE: 3.5 inch, 1.44 Mb floppy disk
- 15 (B) COMPUTER: IBM PC compatible
- (C) OPERATING SYSTEM: PC-DOS/MS-DOS
- (D) SOFTWARE: WinPatin (Genentech)
- (vi) CURRENT APPLICATION DATA:
- (A) APPLICATION NUMBER:
- 20 (B) FILING DATE: 14-Jul-1998
- (C) CLASSIFICATION:
- (vii) PRIOR APPLICATION DATA:
- (A) APPLICATION NUMBER: 08/918874
- (B) FILING DATE: 26-Aug-1997
- 25 (viii) ATTORNEY/AGENT INFORMATION:
- (A) NAME: Marschang, Diane L.
- (B) REGISTRATION NUMBER: 35,600
- (C) REFERENCE/DOCKET NUMBER: P1129R1PCT
- (ix) TELECOMMUNICATION INFORMATION:
- 30 (A) TELEPHONE: 650/225-5416
- (B) TELEFAX: 650/952-9881
- (2) INFORMATION FOR SEQ ID NO:1:
- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 386 amino acids
- 35 (B) TYPE: Amino Acid
- (D) TOPOLOGY: Linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
- Met Gly Leu Trp Gly Gln Ser Val Pro Thr Ala Ser Ser Ala Arg
- 1 5 10 15
- 40 Ala Gly Arg Tyr Pro Gly Ala Arg Thr Ala Ser Gly Thr Arg Pro
- 20 25 30
- Trp Leu Leu Asp Pro Lys Ile Leu Lys Phe Val Val Phe Ile Val
- 35 40 45

	Ala Val Leu Leu Pro Val Arg Val Asp Ser Ala Thr Ile Pro Arg	50	55	60
	Gln Asp Glu Val Pro Gln Gln Thr Val Ala Pro Gln Gln Gln Arg	65	70	75
5	Arg Ser Leu Lys Glu Glu Glu Cys Pro Ala Gly Ser His Arg Ser	80	85	90
	Glu Tyr Thr Gly Ala Cys Asn Pro Cys Thr Glu Gly Val Asp Tyr	95	100	105
10	Thr Ile Ala Ser Asn Asn Leu Pro Ser Cys Leu Leu Cys Thr Val	110	115	120
	Cys Lys Ser Gly Gln Thr Asn Lys Ser Ser Cys Thr Thr Thr Arg	125	130	135
	Asp Thr Val Cys Gln Cys Glu Lys Gly Ser Phe Gln Asp Lys Asn	140	145	150
15	Ser Pro Glu Met Cys Arg Thr Cys Arg Thr Gly Cys Pro Arg Gly	155	160	165
	Met Val Lys Val Ser Asn Cys Thr Pro Arg Ser Asp Ile Lys Cys	170	175	180
20	Lys Asn Glu Ser Ala Ala Ser Ser Thr Gly Lys Thr Pro Ala Ala	185	190	195
	Glu Glu Thr Val Thr Thr Ile Leu Gly Met Leu Ala Ser Pro Tyr	200	205	210
	His Tyr Leu Ile Ile Ile Val Val Leu Val Ile Ile Leu Ala Val	215	220	225
25	Val Val Val Gly Phe Ser Cys Arg Lys Lys Phe Ile Ser Tyr Leu	230	235	240
	Lys Gly Ile Cys Ser Gly Gly Gly Gly Gly Pro Glu Arg Val His	245	250	255
30	Arg Val Leu Phe Arg Arg Arg Ser Cys Pro Ser Arg Val Pro Gly	260	265	270
	Ala Glu Asp Asn Ala Arg Asn Glu Thr Leu Ser Asn Arg Tyr Leu	275	280	285
	Gln Pro Thr Gln Val Ser Glu Gln Glu Ile Gln Gly Gln Glu Leu	290	295	300
35	Ala Glu Leu Thr Gly Val Thr Val Glu Xaa Pro Glu Glu Pro Gln	305	310	315
	Arg Leu Leu Glu Gln Ala Glu Ala Glu Gly Cys Gln Arg Arg Arg	320	325	330
	Leu Leu Val Pro Val Asn Asp Ala Asp Ser Ala Asp Ile Ser Thr			

	335	340	345
	Leu Leu Asp Ala Ser Ala Thr Leu Glu	Glu Gly His Ala Lys Glu	
	350	355	360
5	Thr Ile Gln Asp Gln Leu Val Gly Ser	Glu Lys Leu Phe Tyr Glu	
	365	370	375
	Glu Asp Glu Ala Gly Ser Ala Thr Ser Cys Leu		
	380	385 386	

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 2082 base pairs
 (B) TYPE: Nucleic Acid
 (C) STRANDEDNESS: Single
 (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

15 CCAACTGCAC CTCGGTTCTA TCGATTGAAT TCCCCGGGGA TCCTCTAGAG 50
 ATCCCTCGAC CTCGACCCAC GCGTCCGGAA CCTTTGCACG CGCACAAACT 100
 ACGGGGACGA TTTCTGATTG ATTTTGGCG CTTTCGATCC ACCCTCCTCC 150
 CTTCTC ATG GGA CTT TGG GGA CAA AGC GTC CCG ACC GCC 189
 Met Gly Leu Trp Gly Gln Ser Val Pro Thr Ala
 20 1 5 10
 TCG AGC GCT CGA GCA GGG CGC TAT CCA GGA GCC AGG ACA 228
 Ser Ser Ala Arg Ala Gly Arg Tyr Pro Gly Ala Arg Thr
 15 20
 GCG TCG GGA ACC AGA CCA TGG CTC CTG GAC CCC AAG ATC 267
 25 Ala Ser Gly Thr Arg Pro Trp Leu Leu Asp Pro Lys Ile
 25 30 35
 CTT AAG TTC GTC GTC TTC ATC GTC GCG GTT CTG CTG CCG 306
 Leu Lys Phe Val Val Phe Ile Val Ala Val Leu Leu Pro
 40 45 50
 30 GTC CGG GTT GAC TCT GCC ACC ATC CCC CGG CAG GAC GAA 345
 Val Arg Val Asp Ser Ala Thr Ile Pro Arg Gln Asp Glu
 55 60
 GTT CCC CAG CAG ACA GTG GCC CCA CAG CAA CAG AGG CGC 384
 Val Pro Gln Gln Thr Val Ala Pro Gln Gln Gln Arg Arg
 35 65 70 75
 AGC CTC AAG GAG GAG GAG TGT CCA GCA GGA TCT CAT AGA 423
 Ser Leu Lys Glu Glu Glu Cys Pro Ala Gly Ser His Arg
 80 85
 TCA GAA TAT ACT GGA GCC TGT AAC CCG TGC ACA GAG GGT 462
 40 Ser Glu Tyr Thr Gly Ala Cys Asn Pro Cys Thr Glu Gly

	90	95	100	
	GTG GAT TAC ACC ATT GCT TCC AAC AAT TTG CCT TCT TGC	501		
	Val Asp Tyr Thr Ile Ala Ser Asn Asn Leu Pro Ser Cys			
	105	110	115	
5	CTG CTA TGT ACA GTT TGT AAA TCA GGT CAA ACA AAT AAA	540		
	Leu Leu Cys Thr Val Cys Lys Ser Gly Gln Thr Asn Lys			
	120	125		
	AGT TCC TGT ACC ACG ACC AGA GAC ACC GTG TGT CAG TGT	579		
	Ser Ser Cys Thr Thr Thr Arg Asp Thr Val Cys Gln Cys			
10	130	135	140	
	GAA AAA GGA AGC TTC CAG GAT AAA AAC TCC CCT GAG ATG	618		
	Glu Lys Gly Ser Phe Gln Asp Lys Asn Ser Pro Glu Met			
	145	150		
	TGC CGG ACG TGT AGA ACA GGG TGT CCC AGA GGG ATG GTC	657		
15	Cys Arg Thr Cys Arg Thr Gly Cys Pro Arg Gly Met Val			
	155	160	165	
	AAG GTC AGT AAT TGT ACG CCC CGG AGT GAC ATC AAG TGC	696		
	Lys Val Ser Asn Cys Thr Pro Arg Ser Asp Ile Lys Cys			
	170	175	180	
20	AAA AAT GAA TCA GCT GCC AGT TCC ACT GGG AAA ACC CCA	735		
	Lys Asn Glu Ser Ala Ala Ser Ser Thr Gly Lys Thr Pro			
	185	190		
	GCA GCG GAG GAG ACA GTG ACC ACC ATC CTG GGG ATG CTT	774		
	Ala Ala Glu Glu Thr Val Thr Thr Ile Leu Gly Met Leu			
25	195	200	205	
	GCC TCT CCC TAT CAC TAC CTT ATC ATC ATA GTG GTT TTA	813		
	Ala Ser Pro Tyr His Tyr Leu Ile Ile Ile Val Val Leu			
	210	215		
	GTC ATC ATT TTA GCT GTG GTT GTG GTT GGC TTT TCA TGT	852		
30	Val Ile Ile Leu Ala Val Val Val Val Gly Phe Ser Cys			
	220	225	230	
	CGG AAG AAA TTC ATT TCT TAC CTC AAA GGC ATC TGC TCA	891		
	Arg Lys Lys Phe Ile Ser Tyr Leu Lys Gly Ile Cys Ser			
	235	240	245	
35	GGT GGT GGA GGA GGT CCC GAA CGT GTG CAC AGA GTC CTT	930		
	Gly Gly Gly Gly Gly Pro Glu Arg Val His Arg Val Leu			
	250	255		
	TTC CGG CGG CGT TCA TGT CCT TCA CGA GTT CCT GGG GCG	969		
	Phe Arg Arg Arg Ser Cys Pro Ser Arg Val Pro Gly Ala			
40	260	265	270	
	GAG GAC AAT GCC CGC AAC GAG ACC CTG AGT AAC AGA TAC	1008		
	Glu Asp Asn Ala Arg Asn Glu Thr Leu Ser Asn Arg Tyr			
	275	280		

TTG CAG CCC ACC CAG GTC TCT GAG CAG GAA ATC CAA GGT 1047
 Leu Gln Pro Thr Gln Val Ser Glu Gln Glu Ile Gln Gly
 285 290 295

5 CAG GAG CTG GCA GAG CTA ACA GGT GTG ACT GTA GAG TYG 1086
 Gln Glu Leu Ala Glu Leu Thr Gly Val Thr Val Glu Xaa
 300 305 310

CCA GAG GAG CCA CAG CGT CTG CTG GAA CAG GCA GAA GCT 1125
 Pro Glu Glu Pro Gln Arg Leu Leu Glu Gln Ala Glu Ala
 315 320

10 GAA GGG TGT CAG AGG AGG AGG CTG CTG GTT CCA GTG AAT 1164
 Glu Gly Cys Gln Arg Arg Leu Leu Val Pro Val Asn
 325 330 335

15 GAC GCT GAC TCC GCT GAC ATC AGC ACC TTG CTG GAT GCC 1203
 Asp Ala Asp Ser Ala Asp Ile Ser Thr Leu Leu Asp Ala
 340 345

TCG GCA ACA CTG GAA GAA GGA CAT GCA AAG GAA ACA ATT 1242
 Ser Ala Thr Leu Glu Glu Gly His Ala Lys Glu Thr Ile
 350 355 360

20 CAG GAC CAA CTG GTG GGC TCC GAA AAG CTC TTT TAT GAA 1281
 Gln Asp Gln Leu Val Gly Ser Glu Lys Leu Phe Tyr Glu
 365 370 375

GAA GAT GAG GCA GGC TCT GCT ACG TCC TGC CTG TGAAAG 1320
 Glu Asp Glu Ala Gly Ser Ala Thr Ser Cys Leu
 380 385 386

25 AATCTCTTCA GGAAACCAGA GCTTCCCTCA TTTACCTTTT CTCCTACAAA 1370
 GGGGAAGCAGC CTGGAAGAAA CAGTCCAGTA CTTGACCCAT GCCCCAACAA 1420
 ACTCTACTAT CCAATATGGG GCAGCTTACC AATGGTCCTA GAACCTTTGTT 1470
 AACGCACTTG GAGTAATTTT TATGAAATAC TGCGTGTGAT AAGCAAACGG 1520
 GAGAAATTTA TATCAGATTC TTGGCTGCAT AGTTATACGA TTGTGTATTA 1570

30 AGGGTCGTTT TAGGCCACAT GCGGTGGCTC ATGCCTGTAA TCCCAGCACT 1620
 TTGATAGGCT GAGGCAGGTG GATTGCTTGA GCTCGGGAGT TTGAGACCAG 1670
 CCTCATCAAC ACAGTGAAAC TCCATCTCAA TTTAAAAAGA AAAAAAGTGG 1720
 TTTTAGGATG TCATTCTTTG CAGTTCTTCA TCATGAGACA AGTCTTTTTT 1770
 TCTGCTTCTT ATATTGCAAG CTCCATCTCT ACTGGTGTGT GCATTTAATG 1820

35 ACATCTAACT ACAGATGCCG CACAGCCACA ATGCTTTGCC TTATAGTTTT 1870
 TTAACCTTAG AACGGGATTA TCTTGTTATT ACCTGTATTT TCAGTTTCGG 1920
 ATATTTTGA CTTAATGATG AGATTATCAA GACGTACCCC TATGCTAAGT 1970

CATGAGCATA TGGACTTACG AGGGTTCGAC TTAGAGTTTT GAGCTTTAAG 2020

ATAGGATTAT TGGGGGCTTA CCCCCACCTT AATTAGAAGA AACATTTTAT 2070

ATTGCTTTAC TA 2082

(2) INFORMATION FOR SEQ ID NO:3:

- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CATAAAAGTT CCTGCACCAT GACCAGAGAC ACAGTGTGTC AGTGTAAGA 50

(2) INFORMATION FOR SEQ ID NO:4:

- 15 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CTTCAGGAAA CCAGAGCTTC CCTC 24

20 (2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
25 (D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TTCTCCCGTT TGCTTATCAC ACGC 24